IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Martin et al.
Application No. 10/519,311
Filed: December 22, 2004
Confirmation No. 9128
For: METHOD OF TREATING AUTOIMMUNE DISEASES WITH INTERFERON-BETA AND IL-2R ANTAGONIST
Examiner: Bruce Hissong
Art Unit: 1614
Attorney Reference No. 4239-64111-05

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COMMISSIONER FOR PATENTS

DECLARATION OF DR. ALICE FONG UNDER 37 C.F.R. § 1.132

1. I, Alice Fong, am a medical director in clinical development at PDL BioPharma, Inc. I hold a Pharm.D. degree from the University of California, San Francisco. I completed an internship at St. John's Hospital in Springfield, Il. I have conducted clinical trials for the past 23 years; a copy of my *curriculum vitae* is attached.

2. I have reviewed the pending claims of the above-referenced application, which are directed to treating a subject with multiple sclerosis by administering to the subject a therapeutically effective amount of interferon beta and a therapeutically effective amount of an antibody that specifically binds interleukin-2 receptor, wherein the antibody is administered every other week for two weeks and then monthly, once a week, every other week, or once a month. It is my understanding that claims 1, 3-6, 8-14, 16-17 and 19 are rejected as allegedly being obvious over the "Study for Zenapax" document (htpp://www.ms-network.com/pat/newsflash/show.asp?ID=143), Khoury et al. (Arch. Neurol. 57: 1183-1189, 2000), Paty et al. (Neurology 43: 662-667, 1993) and Jacobs et al. (Ann. Neurol. 39: 285-294, 1996).

3. We have conducted a clinical trial to investigate the effect of concurrent daclizumab and interferon-beta therapy in patients with active relapsing remitting multiple sclerosis (MS). This multi-center, randomized, double-blind, placebo controlled study was performed at 51 sites, both in the U.S. and abroad. A total of 230 patients enrolled in the study. The inclusion criteria were:

(1) males and females, 18-55 years of age

(2) Diagnosis of MS by McDonald criteria

(3) EDSS score of ≤ 5.0

(4) subject on stable interferon-beta regimen for at least six months

(5) subject had at least one MS relapse on interferon beta or a qualifying MRI within 12 months

The patient population was divided randomly into three groups:

(1) daclizumab (Roche Penzberg) at 2 mg/kg subcutaneously every two weeks with concurrent interferon-beta therapy;

(2) daclizumab at 1 mg/kg subcutaneously every four weeks with concurrent interferon beta therapy (a placebo was administered every two weeks, to alternate with daclizumab); and

(3) placebo every two weeks with concurrent interferon beta therapy (control group).

The primary efficacy endpoint was the total number of new or enlarged gadolinium contrast enhancing lesions on monthly brain MRIs between week 8 and week 24 of the study. Serious adverse events (SAEs) were also assessed. A diagram showing the details of the study design is attached as Exhibit A.

Statistical analyses were used to study the efficacy of the treatment regimens. Individuals in Group (1), who received 2 mg/kg daclizumab every two weeks had a 72% reduction ($p=0.004$) in the mean number of new or enlarged gadolinum contrast enhancing lesions as compared to the control group. Individuals in Group (2), who received 1 mg/kg daclizumab every four weeks had a 25% reduction ($p=0.501$) in the mean number of new or enlarged gadolinum contrast enhancing lesions as compared to the placebo control group. Thus, there was a statistically significant reduction in the mean number of new or enhanced lesions in Group (1), who received

2 mg/kg daclizumab every two weeks, and a strong trend in the reduction of Group (2), who received 1 mg/kg daclizumab every four weeks. The extent of this reduction could not have been predicted based on prior results.

In the study population there were 26 patients with 35 SAEs at week 24. About 40% of these SAEs were infections or inflammatory conditions such as esophagitis or cholecystitis. Those SAEs that were assessed as "study drug related" showed the highest frequency with infections (3.9% in the daclizumab treated populations as compared to 0% in the control group). The SAEs that were drug related were highest in Group (1).

The conclusions of the study were that treatment with daclizumab in combination with interferon-beta is more effective than treatment with interferon-beta alone. The preliminary safety profile was within acceptable limits. An abstract describing the results from this study is attached as Exhibit B.

4. The Study of Zenapax describes a study protocol wherein patients will be treated with seven intravenous infusions of Zenapax (daclizumab) over a six month period, and indicates that the subjects will have MRI scans before each infusion. However, one of skill in the art could not have predicted whether daclizumab would have any beneficial effect based on this description. Jacobs et al. and Pary et al. describe the use of interferon-beta to treat MS. Khoury et al. teach that the number of CD25+ T cells is correlated with the gadolinium enhancing lesions in patients with MS. Even if one of skill in the art were to combine the teachings of The Study of Zenapax with Jacobs et al., Paty et al. and Khoury et al., one of skill in the art could not predict the superior results obtained in this clinical trial using the treatment regimens that utilize both daclizumab and interferon-beta.

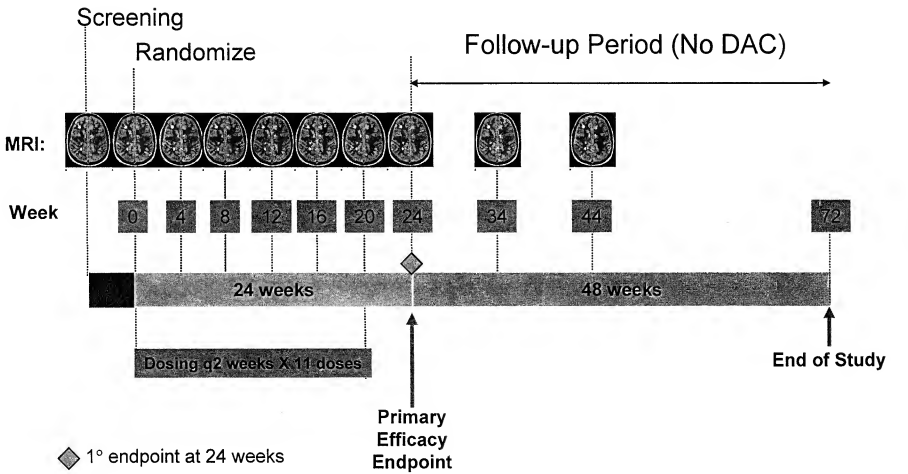
5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Alice Fong
Alice Fong, Pharm.D

18 September 2007
Date

Vall d'Hebron
Hospital
Unitat de Neuroimmunologia Clínica

CHOICE Study Design



All patients on background IFN-beta

EXHIBIT A

Preliminary CHOICE results: A Phase 2, randomized, double-blind, placebo-controlled multi-centre study of subcutaneous daclizumab in patients with active, relapsing forms of multiple sclerosis on interferon-beta

X. Montalban, D. Wynn, M. Kaufman, M. Wang, A. Fong (Barcelona, Spain; Northbrook, Charlotte, Fremont, USA)

Background: Open-label studies of daclizumab (DAC) given to patients with relapsing forms of multiple sclerosis (MS) suggested that DAC reduces the number of new MRI lesions in patients refractory to interferon-beta therapies.

Objectives: To evaluate the efficacy and safety of DAC in a controlled MS trial

Methods: Patients with a confirmed MS diagnosis, an Expanded Disability Status Scale (EDSS) <= 5 at screening, on stable interferon-beta for >= 6 months, and >= 1 relapse or qualifying MRI within 12 months of screening were included. A total of 230 patients were equally randomized to 1 of 3 treatment arms: 2 mg/kg DAC every 2 weeks (high dose), 1 mg/kg DAC every 4 weeks (low dose) or placebo. Study drug was given for 24 weeks with 48 weeks of followup. The primary efficacy endpoint was the total number of new or enlarged gadolinium contrast enhancing lesions (Gd-CELs) on monthly brain MRIs collected from Week 8 to Week 24. A secondary efficacy endpoint was the relapse rate between Weeks 8 to 24. Pharmacokinetics, pharmacodynamics, immunogenicity, and changes in EDSS and MSFC-3 were also assessed. The study is currently ongoing and patients will be monitored to Week 72.

Results: The primary efficacy analysis on the intention-to-treat (ITT) patients showed the mean number of new or enlarged Gd-CELs was significantly reduced by 72% in the 2 mg/kg group (n=75) compared with the placebo group (n=77) (p=0.004). The 1 mg/kg group (n=78) showed a 25% reduction compared with placebo but did not achieve statistical significance.

Based on data up to Week 24, the relapse rate analysis on the ITT population indicates that both DAC regimens reduced the annualized relapse rate by approximately 35 % compared to placebo, but did not reach statistical significance. The study was not powered for the relapse rate endpoint.

Preliminary safety data showed a similar overall infection rate across all treatment groups; however, the overall incidence of serious infections was higher in the 2 mg/kg group. Urinary tract infections were slightly higher with the 2 mg/kg dose (17% vs 13% placebo). The incidence of cutaneous events was higher in the combined DAC groups (34% DAC vs 27% placebo) and often appeared during the washout phase. The nature of the cutaneous events varied but improved with standard treatment.

Conclusions: The addition of DAC 2 mg/kg q2 weeks to beta interferon was associated with a statistically significant reduction of Gd-CELs and a favourable trend in reducing relapse rates. In general, DAC was safe and well tolerated in this beta interferon treated MS population.

EXHIBIT B

Alice Fong, PharmD, MBA

EDUCATION

1997- 2001	Golden Gate University	M.B.A.
1982-1983	St. John's Hospital Springfield, Illinois	Hospital Pharmacy Residency – Certificate
1978-1982	University of California School of Pharmacy San Francisco, California	Pharm. D.
1974-1976	University of California Davis, California	B. S. Biochemistry
1972-1974	Sacramento City College Sacramento, California	A. S. Math and Science

PROFESSIONAL EXPERIENCE

2005- Present	Medical Director, Clinical Development PDL BioPharma, Fremont, California
2003-2005	Associate Director, Medical Affairs FibroGen, South San Francisco, California
2001-2002	Group Director, Pharmacovigilance Operations/Account Executive Sentrx (Little Falls, NJ) Sunnyvale, California
1995-2001	Associate Director, Clinical Science, Cellcept/Zenapax Transplant Team Roche Global Development, Palo Alto, California
1994	Associate Director, Clinical Research, Cardiovascular Syntex, Palo Alto, California
1991-93	Senior Clinical Research Scientist, Clinical Research Department Marion Merrell Dow, Kansas City, Missouri Therapeutic areas: CNS – MAO B Inhibitor Cardiovascular – Posicor - angina
1987-91	Clinical Research Manager, Department of Clinical Research & Development, Hoffmann-La Roche, Inc., Nutley, New Jersey
1984-87	Senior Clinical Research Associate, Department of Clinical Research & Development, Hoffmann-La Roche, Inc., Nutley, NJ
1986-1991	Per Diem Pharmacist St. Mary's Hospital, Passaic, New Jersey

1985	Relief Pharmacist Clifton Pharmacy, Clifton, New Jersey
1983-84	Clinical Pharmacist University of Maryland Cancer Center, Baltimore, Maryland

PUBLICATIONS

1. X. Montalban, D. Wynn, M. Kaufman, M. Wang, A. Fong. Preliminary CHOICE Results: A Phase 2, randomized, double-blind, placebo-controlled multicentre study of subcutaneous daclizumab in patients with active, relapsing forms of multiple sclerosis on interferon-beta. ECTRIMS, October 2007
2. P. Urquilla, A. Fong, S. Oksanen, S. Leigh, E. Turtle, L. Flippin, M. Brenner, E. Muthukrishnan, P. Fourney, A. Lin, D. Yeowell, C. Molineaux. Upregulation of Endogenous Erythropoietin (EPO) in Healthy Subjects by Inhibition of Hypoxia Inducible Factor (HIF) Prolyl Hydroxylase. Blood 2004;104:11, Nov. 15, 2004
3. Urquilla P, Fong A, Oksanen S, Leigh S, Turtle E, Flippin L, Brenner M, Muthukrishnan E, Fourney P, Lin A, Yeowell D, Molineaux C. Upregulation of Endogenous EPO in Healthy Subjects by Inhibition of HIF-PH (abstract SU-PO062). J Am Soc Nephrol 2004;15: 546A
4. G. Raghu, MD, Y. Mageto, MD, K. Flaherty, MD, K. Brown, MD, A. Fong, PharmD. Safety and Tolerability of Human Monoclonal Antibody FG-3019, Anti-Connective Tissue Growth Factor, in Patients with idiopathic pulmonary fibrosis. CHEST 2004;126(4): 773S
5. Bunchman T, Navarro M, Broyer M, Sherbotie J, Chavers B, Tonshoff B, Birk P, Lerner G, Lirenman D, Greenbaum L, Walker R, Zimmerhackl LB, Blowey D, Clark G, Ettenger R, Arterburn S, Klamerus K, Fong A, Tang H, Thomas S, Ramos E., The use of mycophenolate mofetil suspension in pediatric renal allograft recipients. Pediatr Nephrol. 2001;16(12):978-84.
6. Ettenger R, Warshaw B, Mentser M, Roberts J, Arterburn S, Fong A, Ramos E. Long-Term Safety and Efficacy of Oral Mycophenolate Mofetil in Pediatric Renal Transplant Recipients. Pediatric Transplantation 2001.
7. Ribner H, Stasior C, Molteni A, Fong A, et al: Acute Hemodynamic and Hormonal Effects of Cilazapril, A New, Long-Acting Angiotensin Converting Enzyme Inhibitor in Congestive Heart Failure. Clinical Research 1987; 35: 319A.
8. Fong A, Dunton A, et al: Acute Hemodynamic Response to Oral Cilazapril in Congestive Heart Failure. Clin. Pharm. Ther. February 1987.
9. Fong A: Formulary of Pharmaceutical Products, St. John's Hospital, Springfield, Illinois, 1983.
10. Pratt CM, Fong A, et al: Recent Advances in the Understanding of Ambulatory Electrocardiography. Clinical Cardiology 1979; 1:217.
11. Pratt CM, Fong A, et al: Quantitative Variability of Ventricular Ectopic Activity Detected by Consecutive 24-hour Ambulatory Monitoring. Clinical Research 1978; 26: 260A.
12. Salel AF, Fong A, et al: Accuracy of Coronary Profile: Correlation of Arteriography with Risk Factors. N Engl J Med 1977; 296: 1447.

PRESENTATIONS

October 2004	Data Safety Monitoring Board (DSMB) Meeting, South San Francisco, CA
October 2003	Data Safety Monitoring Board (DSMB) Meeting, South San Francisco, CA
June 2003	Multicenter FG-3019 IPF Investigators' Meeting, South San Francisco, CA
April 2002	Pharmacovigilance Training Course, Wayne, New Jersey

April 2000	Multicenter Mycophenolate Mofetil Pediatric Renal Transplantation Investigators' Meeting, presentation of one-year data, Sonoma, California
April 1998	Panel participant in Industry Forum "Opportunities for PharmDs in the Pharmaceutical Industry" at University of California at San Francisco School of Pharmacy, San Francisco, California
June 1997	Multicenter Mycophenolate Mofetil Pediatric Renal Transplantation Investigators' Meeting, Miami, Florida
May 1994	Multicenter Ranolazine Intermittent Claudication Investigators' Meeting San Juan, Puerto Rico
October 1992	Multicenter Posicor Angina Investigators' Meeting, 1992 Kansas City, MO
March 1992	Faculty of Xavier College of Pharmacy in New Orleans, Louisiana, "Opportunities for Pharm Ds in Pharmaceutical Industry"
October 1991	Annual Meeting of California Society of Hospital Pharmacists; Long Beach, CA. Title: "Clinical Research in Industry"
April, 1988	Multicenter Cilazapril CHF Investigators' Meeting; Nutley, New Jersey
March 1987	Poster, Acute Hemodynamic Response to Oral Cilazapril in Congestive Heart Failure, 88th Annual Meeting of ASCPT; Orlando, Florida
February 1984	Pharmacy staff of UMCC in Baltimore, Maryland. Title: "Hepatamine"
September1983	Faculty of Xavier College of Pharmacy in New Orleans, Louisiana. Title: "Ethmozin: An Effective New Antiarrhythmic Drug"
September1983	Oregon Health Sciences University Hospital in Portland, Oregon. Title: "Ethmozin: An Effective New Antiarrhythmic Drug"
August, 1983	Faculty and staff of University of Georgia in Athens, Georgia. Title: "Ethmozin"
August, 1983	Faculty of University of Arizona College of Pharmacy,Tucson, AZ, "Ethmozin"
April, 1983	Faculty and students of Creighton University School of Pharmacy in Omaha, Nebraska, "Ethmozin"
March, 1983	Faculty of Wayne State University School of Pharmacy in Detroit, MI, "Ethmozin"
March, 1983	Faculty/students of Howard University College of Pharmacy in Washington, DC. Title: "Quality Assurance"

MEMBERSHIPS - PROFESSIONAL ORGANIZATIONS

American Society of Health System Pharmacists (ASHP)
California Society of Hospital Pharmacists (CSHP)
Drug Information Association (DIA)

AWARDS AND HONORS

2000	Spot Award, Roche Global Development
1991	Management Incentive Bonus, Hoffmann-La Roche
1989	Management Incentive Bonus, Hoffmann-La Roche
1988	Management Incentive Bonus, Hoffmann-La Roche

PHARMACY LICENSE STATUS

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